Imaging the Addicted Brain: From Molecules to Behavior

It is a pleasure and an honor for me to deliver this year's Henry Wagner lecture. For most of my professional research career, I've made use of nuclear medicine imaging technologies to investigate the effects of drugs in the human brain. Today, as director of the National Institute on Drug Abuse (NIDA), I often start my talks by noting the dramatic escalation and wide-ranging tolls of drug abuse and addiction. In this country alone, the costs associated with the consequences of drug abuse including alcohol are estimated to be $486 billion a year. Addiction is one of the medical consequences of drug abuse, but drug abuse also contributes significantly to the burden of many medical diseases. In addition, drug abuse and addiction have devastating social consequences that range from loss of work, poor school performance, and family disintegration to criminal behaviors.

Drug addiction is a disease for which we can target the vector: the drug. It is clear, however, that although chronic drug administration is a requirement for producing addiction, drugs themselves are not the only variables involved. Other variables are at work, some enabling and some protecting against the process of addiction. We know that biology is extremely important—genetics can make an individual more vulnerable or alternatively more resilient to the effects of drugs. We also know that past developmental history, such as conduct problems while growing up, may make some individuals more vulnerable. And we have come to understand that environmental factors—particularly stress—play an extremely important role in facilitating drug addiction.

Why do people take drugs? People take drugs because they want to change their mental state; they want to feel good; or they want to feel better. Why is it that some drugs may be expected to have such an effect? Years of research, initially in laboratory animals, have shown us that one of the characteristics that is indispensable for drugs to have this effect is their ability to increase brain dopamine concentration in areas that form part of the limbic circuit. Research has shown that dopamine is a neurotransmitter that is involved in the regulation and motivation of behaviors that are indispensable for survival. So, for example, food, which we need in order to survive, increases dopamine, which in turn motivates and drives us to learn that it is salient and to engage in behaviors that result in obtaining food. Similarly, dopamine provides the drive for sexual behaviors that are ultimately necessary for the reproduction of the species. It also drives the motivation for our gregarious behavior that results in the social interactions that also facilitate the chances of our species' survival. Drugs of abuse target the same mechanisms; that is, increasing dopamine, but they do it at a greater magnitude and duration than natural reinforcers. This ability of drugs to directly increase dopamine—the same mechanism that nature uses to enhance and motivate our behavior—is considered to be crucial for their reinforcing effects. That is, drugs of abuse engage the neurobiological mechanisms by which nature ensures that behaviors that are indispensable for survival motivate the procurement of more drugs and, with repeated administration, can result in addiction.

Nora Volkow, MD, Director of the National Institute on Drug Abuse, delivered the Henry Wagner lecture at a plenary session on June 20 at the SNM Annual Meeting in Philadelphia, PA.

Although increases in dopamine are important in reinforcing the effects of drugs, by themselves such increases do not adequately explain addiction. Addiction, as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (IV), is the condition that emerges from chronic drug use that leads to the compulsive administra-

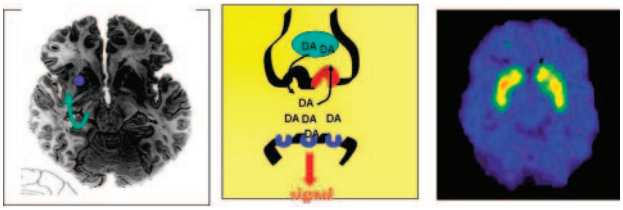

FIGURE 1. (A) Anatomy; (B) dopamine (DA) synapse; (C) DA D_2 receptors.

tion of the drug despite the fact that the subject may no longer want to take it and even at the expense of seriously adverse consequences. However, if you were to give drugs to a person who is not addicted, you would see an increase in dopamine in his or her brain that would be equal to or even larger than that seen in the brain of an addicted individual. So, the ability of drugs of abuse to increase dopamine by itself does not explain the process of addiction.

What is the role of dopamine in producing the loss of control seen in the addicted person? My colleagues and I at Brookhaven National Laboratory (BNL) have used PET to investigate the involvement of the brain dopamine system in a wide variety of drug addictions. In this talk, I will concentrate on one of the proteins we have investigated that is involved in dopamine neurotransmission; namely the dopamine D_2 receptors. The dopamine cells reside in the mesencephalon (Fig. 1), from which they send projections to the areas of the brain they modulate. When dopamine cells fire, they release dopamine, and this message is transmitted by postsynaptic dopamine receptors. One of the dopamine receptors that has been shown to be important in the reinforcing effects of drugs of abuse is the dopamine D_2 receptor. We have used: [^{18}F]*N*-methylspiroperidol as well as ^{11}C-raclopride as dopamine D_2 receptor ligands to measure dopamine D_2 receptors in addicted individuals. We have shown that dopamine D_2 receptor availability is significantly decreased across a wide variety of types of drug addictions. Moreover, these

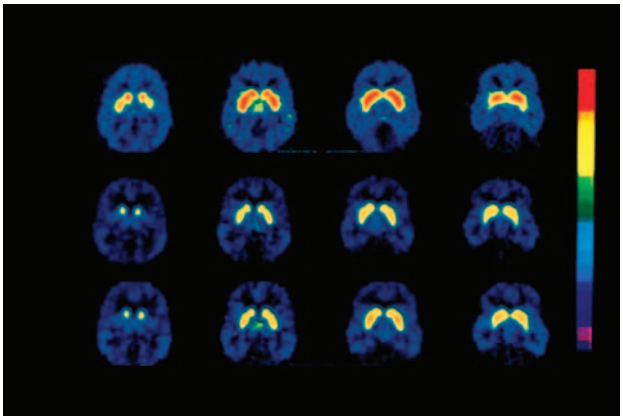

FIGURE 2. Effect of cocaine abuse on dopamine D_2 receptors. Top row: normal subject; middle row: cocaine abuser (1 month after cessation of use); bottom row: cocaine abuser (4 months after cessation of use).

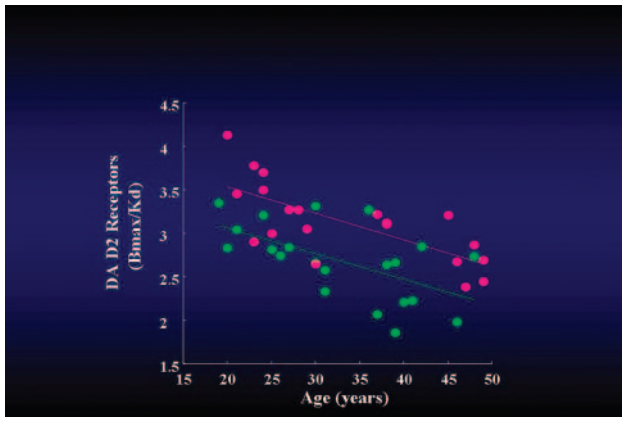

FIGURE 3. Dopamine D_2 receptors in controls and in cocaine abusers. Pink = normal controls; green = cocaine abusers.

decreases are observed both during early drug withdrawal and after protracted drug detoxification, as shown in the brain images obtained from a study that measured D_2 receptor availability in cocaine abusers at 1 month and at 4 months after last cocaine use (Fig. 2). The individual measures for D_2 receptor availability are shown in this graph (Fig. 3) in green for the cocaine abusers and in pink for the controls. The measure of D_2 receptor availability (obtained with [^{18}F]*N*-methylspiroperidol) is plotted as a function of age since dopamine D_2 receptors in the brain decrease at a rate of approximately 4%–6% per decade. The graph clearly shows that, as a group, cocaine abusers have significant reductions in dopamine D_2 receptors. We have found that these reductions exist whether subjects are tested 1 week after their last use of cocaine or 4–6 months after last utilization. Reductions in dopamine D_2 receptors, then, are long lasting. Such reductions are by no means specific to cocaine. We and others have also documented dopamine D_2 reductions in alcoholic individuals with family histories of alcoholism. Similar findings have been reported in heroin, and we recently reported the same pattern for methamphetamine addiction (Fig. 4).

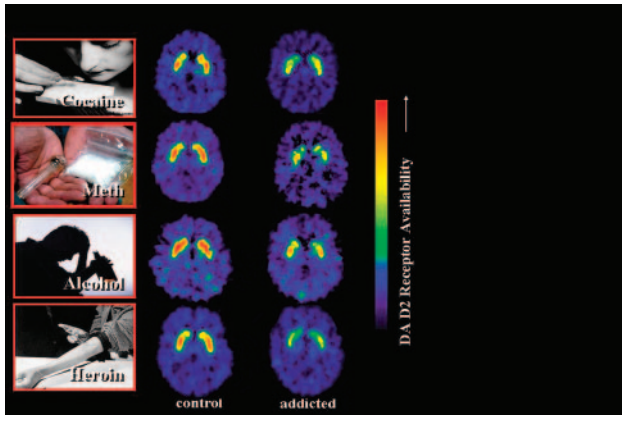

FIGURE 4. Dopamine D_2 receptors are lower in individuals with addictions.

FIGURE 5. (A) Non-drug abuser; (B) drug abuser.

What does this reduction in dopamine D_2 receptors tell us about their involvement in drug addiction? Consider the physiological function of dopamine cells. Fig. 5 represents a dopamine synapse in a normal and in an addicted individual. Dopamine cells function as a mechanism to signal what is salient, so that we can shift our attention to those behaviors that are extremely important for survival. What things are salient? Pleasure is salient, because that's the way nature promotes and motivates us to eat, for example. Aversive things are salient, because that's the way nature teaches us that certain objects, smells, tastes, or actions may be harmful. Things that are novel or unexpected are salient, because by separating out the novel from the routine we can optimize our resources and be on guard for discontinuities rather than constantly scanning the environment. Dopamine self-fires to signal these salient factors. The dopamine that is released into the synapse has a limited time to interact with the receptors, because it is rapidly brought back into the terminal by the dopamine transporters. Mathematical modeling suggests that any given dopamine molecule will stay in the synapse less than 50 milliseconds. The probability of dopamine interacting with a receptor in this brief time period is a function of 2 factors: how much dopamine is liberated in the synapse and how many receptors are available. In a person who is addicted, the dopamine cells may fire, but the probability of an interaction is going to be significantly reduced because receptors are significantly lower in such an individual. So, it is much less likely that the individual will experience an activation by a salient stimuli. In this way, the addicted person learns that natural reinforcers are no longer exciting or motivating (the changes in dopamine are not large enough to signal them as salient stimuli).

What about drugs? Drugs increase dopamine in both quantitatively and qualitatively different ways from natural stimuli. Increases in dopamine in the synapse are 5–10 times greater with drugs than with natural reinforcers. Moreover, drugs such as cocaine, amphetamine, and methamphetamine block the transporter that quickly recycles dopamine back into the terminal. The result is that with drugs, dopamine stays in the synapse for a longer period of time than for natural reinforcers. Thus, despite the fact that the number of receptors is decreased in a drug abuser, the probability of interaction from a drug is very high, not only because the dopamine concentration is very large but also because dopamine's residence time in the synapse is long. The drug abuser learns that while natural reinforcers are no longer able to produce a signal of saliency, drugs of abuse do—a fact that drives and motivates subsequent behavior.

How do we know the extent to which these decreases in receptors are the consequences of chronic drug administration? How do we know that they were not there before the subject became addicted and, hence, rendered him or her more vulnerable to addiction? The answer is that we don't know. The only way to answer this question is to test the subjects *before* they become addicted—an extremely expensive and challenging undertaking. Yet, such an effort is important, because it addresses the issue of what makes a person more vulnerable to drugs of abuse. We decided to investigate this question by looking at the data from another perspective. Here I show the results from another study where we measured dopamine D_2 receptors with ^{11}C-raclopride PET in cocaine abusers and in controls (Fig. 6). The results are the same; cocaine abusers (represented in green) have lower D_2 receptor availability than controls (represented in purple). In this case, however, focus on the normal controls. As noted previously, we lose D_2 receptors as we age. But look at the variability in the levels of dopamine D_2 receptors among control subjects regardless of their ages. Individuals in their early 30s, for example, showed an almost 50% variability in the availability of receptors.

The questions that follow from such an observation are: If low dopamine D_2 receptors are associated with drug addiction, what does it mean to be a person who is *not* addicted but has low levels of these receptors? How does that low expression affect an individual's responses to drugs of abuse? To address these questions, we conducted a relatively straightforward study. We took 23 healthy controls and measured dopamine D_2 receptor

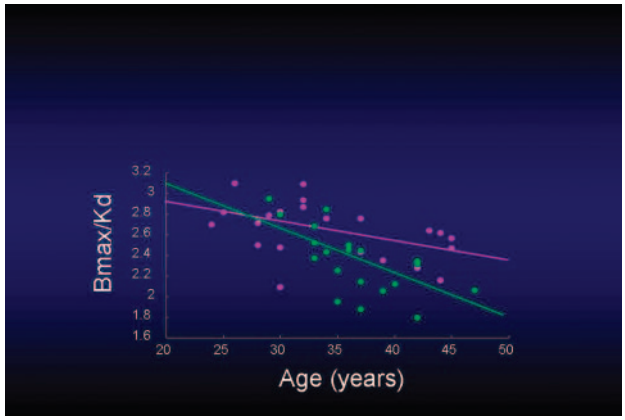

FIGURE 6. Dopamine D_2 receptors in controls and cocaine abusers (^{11}C-raclopride). Purple = normal controls; green = cocaine abusers.

availability. We then administered intravenous methylphenidate, which is a stimulant drug that, like cocaine, increases dopamine by blocking the dopamine transporter, to each of the individuals and asked a simple question: how did they like the effects experienced with this stimulant? Approximately 50% of the individuals liked the way that the injected methylphenidate made them feel, and approximately 50% did not. This contrasts with the results we have obtained in cocaine abusers, all of whom (expect for 1 subject) reported the effects of intravenous methylphenidate to be extremely pleasurable. Why then the variability among the normal controls? We found that this variability was in part related to the expression of dopamine D_2 receptors in these individuals (Fig. 7). In the upper panel is an image representing dopamine D_2 receptor availability measured in a control subject who reported the effects of the drug as unpleasant, and in the lower panel is an image from a control subject who reported these effects as pleasant. The subject who reported the drug as pleasant had lower receptor availability than the subject who reported it as unpleasant. To the right of the figure is the plot of the individual data showing that subjects that reported the effects of methylphenidate as pleasurable had significantly lower levels of D_2 receptors than individuals who reported the effects as unpleasant. (I might note that there are 2 outliers who did not feel the effects of the drug that are extremely interesting but beyond the scope of this lecture.)

Individuals who reported the effects as unpleasant had significantly higher levels of dopamine D_2 receptor availability than those who reported it as pleasant. Indeed, in some subjects in the latter group, receptor availability measures were indistinguishable from those that we have seen in addicted individuals. Why is this an interesting finding? First, it demonstrated the obvious fact that the effects of a drug are not merely a function of the pharmacologic action of the drug but of the unique interaction between the drug and the biochemical characteristics of the subject's brain. In this case, the biochemical target that appears to modulate methylphenidate's reinforcing effects (as experienced by pleasurable responses) is the dopamine D_2 receptors.

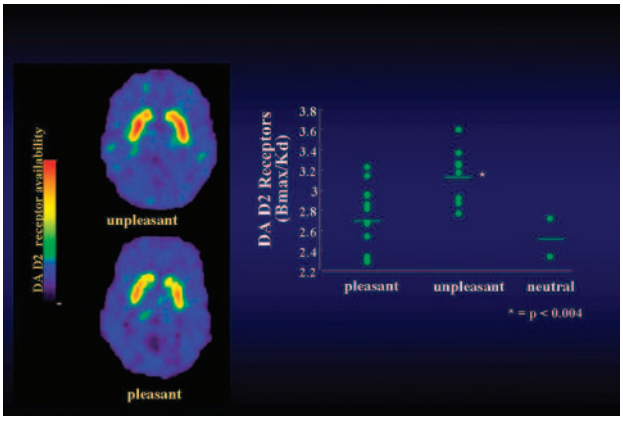

FIGURE 7. Dopamine D_2 receptors and response to intravenous methylphenidate (MP) in controls. Subjects with low receptors report MP as pleasant and those with high receptors as unpleasant.

But why would subjects with high levels of receptors report the drug as unpleasant whereas those with lower receptor levels tended to report it as pleasant? The simplest of explanations is derived from knowledge gained by studies in laboratory animals, where electrical stimulation of different pleasure centers in the brain has been widely used. One of those pleasure centers is the posterior hypothalamus. It has been demonstrated that animals will press a lever to deliver current into the posterior hypothalamus. What's interesting, however, is that if the current is too weak, the animal will not press the lever, because the current is not sufficiently reinforcing to motivate the behavior. If the current is too high, the animal stops pressing the lever, because the current becomes aversive. So, there appears to be an optimal window for electrical stimulation to be perceived as rewarding. Too little and the sensation is not sufficient; too much and it becomes aversive. Using these observations, it is possible to arrive at a similar explanation for why human subjects with high levels of dopamine D_2 receptors experience the effects of methylphenidate intravenously as unpleasant. For individuals with high levels of receptors, intravenous methylphenidate produces a significant increase in synaptic dopamine, pushing them to a threshold at which the experience is aversive. On the other hand, in individuals with low levels of D_2 receptors, the low levels will attenuate the large dopamine increases induced by methylphenidate, bringing it into the "pleasurable" window level.

In human imaging studies, we often make associations that guide us to the answers to significant questions. In this case, we're postulating that perhaps what's going on is that high levels of D_2 receptors make the experience aversive because they exceed a specific threshold. How do we test this? Such an experiment should be simple. Would subjects who perceive the effects as aversive still do so if they were given only 1/10 of the original dose? Would lowering the dose significantly make the experience pleasant? To test this hypothesis, we called the individuals in our original study back for a low dose of intravenous methylphenidate. But they refused, precisely because the original experience had been so aversive. So we don't have an answer to this question. For now, we can say that we believe that low levels of receptors either make individuals more vulnerable to taking drugs, because the experience is pleasant and hence the probability of trying it again is going to be much higher, or, alternatively, that high levels of receptors may protect against drug abuse, since the reaction to the drug will tend to be aversive, decreasing the probability of taking the drug again. One could interpret these results either way. Either low levels of receptors make the individual more vulner-

able or, alternatively, high levels of dopamine D_2 receptors are protective against self-administration of high doses of drugs of abuse (the hypothesis I favor).

How do you test this hypothesis? One method would be to increase dopamine D_2 receptors in the subjects who reported the effects as pleasant. If the hypothesis is correct that high levels of receptors are protective, then the subjects would now experience the effects as unpleasant. The problem is that we don't know how to noninvasively increase dopamine D_2 receptors in the human brain. But we can do this in animals. This is a perfect example of a situation in which an imaging technology such as PET can provide information that can guide us to experiments in animals that will help find causal associations from findings in humans. In this study from BNL, Dr. Peter Thanos began by training rats to self-administer alcohol. He then stereotaxically injected into the striatum an adenovirus into which he had introduced a dopamine D_2 receptor gene. The adenovirus increased dopamine D_2 receptors in the rat brain by 50%. The effect was not long lasting, because the adenovirus does not incorporate the gene into the chromosome. By day 10, the dopamine D_2 receptor levels were back at baseline. On day 20, he again administered the adenovirus with the receptor gene, and again the receptors went up (Fig. 8). The question, of course, is whether these changes in receptor levels modified the levels of alcohol intake. The answer was a dramatic "yes." On day 4 after the initial administration, when the dopamine D_2 receptors were at their highest levels, alcohol intake was reduced by almost 70%. It was not eliminated entirely, but it was dramatically reduced. As the receptors returned to baseline, alcohol consumption returned to its previous levels. After the second injection of the adenovirus, alcohol intake was again dramatically reduced. (You can see in blue in Fig. 8 the results from the animals that were treated with an adenovirus that did not contain a gene, which was done to ensure that the modification in behavior was not the result of another factor, for example, an inflammatory reaction to the viral injection.) Over all, Thanos' results showed that increasing dopamine D_2 receptors does, in fact, regulate the self-administration of alcohol. He has recently replicated these findings in cocaine administration. In addition, he has verified these findings in rats that have been inbred for a predisposition to self-administer alcohol. In these animals with genes that make them vulnerable to consuming alcohol, increasing dopamine D_2 receptors protects them against consuming large quantities of alcohol. It appears that dopamine D_2 receptors are actually interfering with the administration of high doses of drugs—which is what drug addiction and alcoholism are all about.

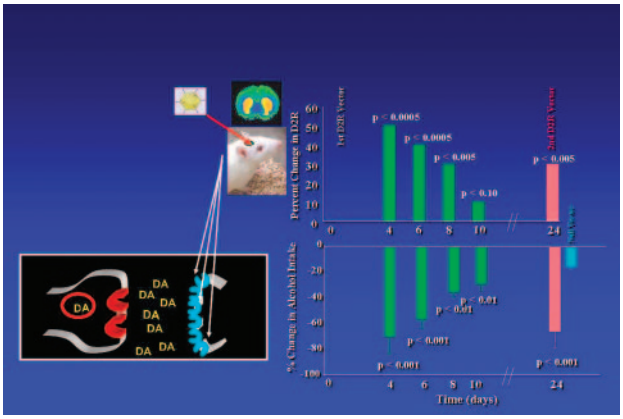

FIGURE 8. Effects of treatment with an adenovirus carrying a dopamine (DA) D_2 receptor gene into NAc in DA D_2 receptors. Reprinted, with permission, from Thanos PK, Volkow ND, Freimuth P, et al. Overexpression of DA D_2 receptors reduces alcohol self-administration. *J Neurochem.* 2002;78:1094–1103.

What causes an individual to have high or low levels of dopamine D_2 receptors? Genes are the most obvious answer. We all know this, and it is an explanation that has been given for a number of years. I still believe that genes are an important contributor in determining the levels of expression of dopamine D_2 receptors in the brain, but other factors must also be taken into account. The environment, for example, plays an extremely important role. Imaging technologies have allowed us for the first time to begin to look at the significant interactions between environment, brain neurobiology, and behavior. The example that I'm going to show is from Drake Morgan and his colleagues at Wake Forest. They measured dopamine D_2 receptors in a group of macaque monkeys and then attempted to determine to what extent change in environmental surroundings could affect expression of these receptors and subsequent self-administration of drugs. Why are such questions important? Because epidemiologic studies have indicated again and again that one of the environmental predictors of risk for drug abuse and addiction is poverty and its attendant social stressors.

Morgan's study looked first at questions of social hierarchy and dopamine D_2 receptors and then at related questions about drug self-administration. For primates, one of the most powerful drives is social reinforcement. In this study, each of the monkeys was raised in isolation, and dopamine D_2 receptor levels were measured. The monkeys were then placed in a group, where a natural social hierarchy was allowed to form. Dopamine D_2 levels were then measured again. The researchers were curious about whether receptor levels in any way could predict placement in the social hierarchy. A previous study by the same group showed that dominant monkeys had higher levels of dopamine D_2 receptors than subordinates. The question here was whether hierarchical position was somehow predetermined by levels of dopamine D_2 receptors in the brain. The somewhat surprising answer was that they could not predict which animals would be dominant or subordinate based on the receptor levels measured when the monkeys still lived in isolation. Instead, once the animals were placed in a group situation in

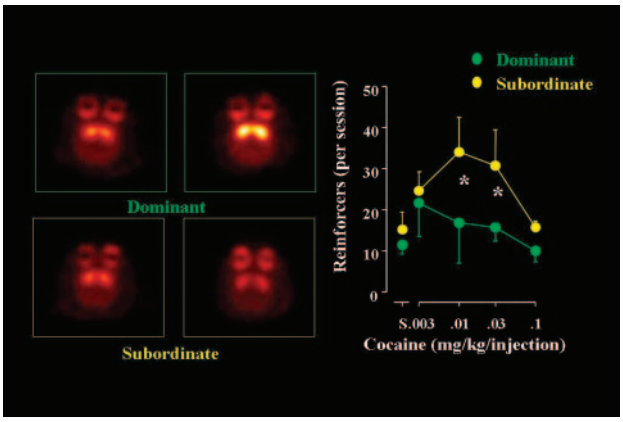

FIGURE 9. Left: animals housed individually; right: animals housed in a group. Reprinted, with permission, from Morgan D, Grant KA, Gage HD, et al. Social dominance in monkeys: dopamine D_2 receptors and cocaine self-administration. *Nat Neurosci. 2002;5:169–174.*

which a hierarchy evolved, dominant animals showed significant increases in dopamine D_2 receptors in their brains, whereas subordinate animals did not (Fig. 9). Thus, if you compared these dominant and subordinate animals in this group with no *a priori* knowledge, you would conclude that dominant animals have significantly higher levels of dopamine D_2 receptors. But this higher level was not there before they became dominant but was triggered instead by an environmental social intervention.

What about their drug taking? The investigators took the same animals and put them into a cocaine self-administration protocol in which the animal pressed a lever to get cocaine. Different doses of cocaine were administered. In Figure 9, the dominant animals are in green. None of the lever presses among these animals reached statistical significance (i.e., none of the animals self-administered cocaine to any significant level). The highest level chosen among these animals was actually the lowest dose available. Compare that with the actions of the subordinate animals, which had low levels of D_2 receptors. These animals readily self-administered relatively high doses of cocaine. This study showed not only the clear association between low levels of dopamine D_2 receptors and vulnerability to drug abuse, but the apparent role of high levels of dopamine D_2 receptors as a protection against the self-administration of high doses of drugs. This brings to light the very interesting suggestion that the environment, in this case a social variable, produces neurobiologic changes in the brain. In this case, those changes occur in mechanisms that we know are important in regulating the administration of drugs.

The effects of drugs are not limited to the devastating consequences of addiction. They also are significant contributors to other diseases. They can produce brain toxicity either by their deleterious effects on blood flow in the brain, or through direct neurotoxic effect to neurons. Drugs are currently one of the main contributors to the AIDS epidemic across the world. Drugs also contribute to cancer, cardiopulmonary diseases, and mental illness, and new data are showing that they may contribute to obesity. Brain imaging plays an extremely important role in trying to understand the mechanism by which drugs of abuse contribute to these diseases and outcomes.

Let's look at neurotoxicity and methamphetamine as an example. Methamphetamine has caused a great deal of concern, because animal studies have revealed that it damages dopamine terminals and in some instances it can lead to dopamine cell death. We engaged in an investigation to determine to what extent the same types of damage were occurring in the brains of people abusing methamphetamine. We also wanted to determine whether damage to dopamine terminals resulted in functional consequences. We found (and it has been validated by others) that by using a ligand that binds to dopamine transporter as a marker of terminals, in this case ^{11}C-d *threo* methylphenidate, that methamphetamine abusers experienced significant reductions in dopamine transporters. This is visible in the striatum in Figure 10. Moreover, we showed that these reductions in dopamine transporters were functionally significant. The lower the transporters, the worse these subjects performed in tasks related to motor speed, whether it was gross motor speed (how quickly they could walk a line) or very fine motor tasks (placing pins in little holes). It was also associated with impaired memory; the lower the level of transporters, the harder it was for subjects to remember words they had heard before. Methamphetamine, then, was neurotoxic to the human brain, and this was producing dysfunction in behavior.

What was also very intriguing and worrisome was that these types of abnormalities are also tied to those reported in Parkinson's disease, where you also see a reduction in dopamine transporters (although the region in the striatum is slightly different). Studies of patients with Parkinson's disease show reductions in dopamine transporters linked with motor slowing and memory impairment. The question that follows is whether methamphetamine users are

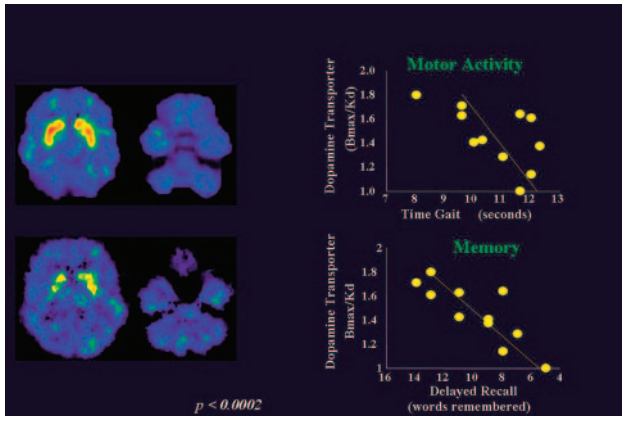

FIGURE 10. Dopamine transporters in methamphetamine abusers. Top: normal control; bottom: methamphetamine abuser.

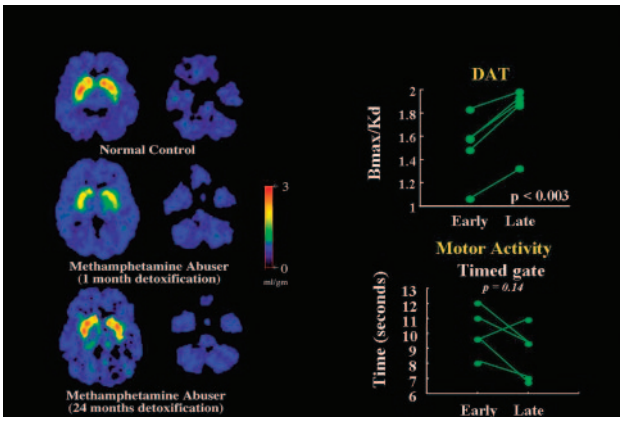

FIGURE 11. Effects of methamphetamine detoxification on dopamine transporters and on motor activity.

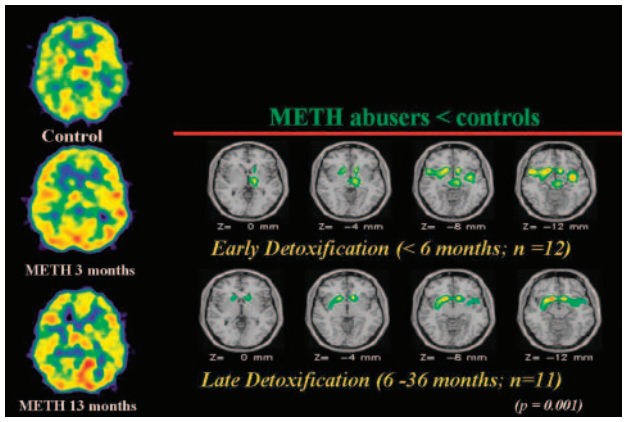

FIGURE 12. Effects of methamphetamine detoxification on brain metabolism.

putting themselves at higher risk of developing neurodegenerative diseases such as Parkinson's when, as part of aging, they will lose more dopamine terminals. One would predict that methamphetamine abusers would be at higher risk for Parkinsonism if the changes are irreversible. However, if the changes in the dopamine terminals recover after cessation of abuse, perhaps these individuals are not inevitably at risk.

This, again, is something that could be evaluated with imaging. It is extremely difficult to get methamphetamine abusers to stop taking this very addictive drug. We looked at a group of 15 parolees, for whom abstinence from drug use was a monitored condition of continued freedom from jail. Only 5 individuals were able to stay clean, despite the serious consequences—a powerful indicator of how malignant drug addiction can be. These 5 individuals who stayed methamphetamine-free underwent PET imaging, as did a group of controls. To my surprise, we saw significant recovery in the expression of dopamine transporters in the brains of these individuals after 9 months of detoxification (Fig. 11). All 5 of the subjects showed an increase in transporters in striatum. However, the recovery of motor function did not reach this level of significance. Recovery in the biochemical parameter was significant, with a somewhat less marked trend toward improvement in motor function.

What does this mean? This evidence suggests that recovery of normal biochemistry may not be sufficient to restore previous normal function. Indeed, although the dopamine transporters showed significant recovery, brain glucose metabolism in many areas remained deficient. This was measured in a crossover study designed to attempt to get information on a larger sample of detoxified methamphetamine abusers. This is shown in these images of the areas of the brain in which methamphetamine abusers had significantly lower metabolic activity than comparable controls (Fig. 12). The top panel shows subjects who had been detoxified for less than 6 months, and the bottom panel, subjects that had been detoxified for 6–36 months. In the early detoxification group, metabolic activity decreases are seen throughout the caudate, nucleus accumbens, thalamus, and mesencephalon. In the protracted detoxification group, significant recovery can be seen in the thalamus, but activity in nucleus accumbens remains significantly decreased, even in individuals as much as 3 years into detoxification. These reductions in activity in the nucleus accumbens are likely to play a very important role in the dysphoria, depression, and anhedonia that methamphetamine abusers continue to experience even after months of detoxification.

However, I'm going to discuss results that I normally would not show, because I do not know yet their functional significance. Fig. 13 shows, in the same group of methamphetamine abusers, the areas of the brain that had increased metabolic activity when compared with control subjects both during early and protracted detoxification. During early detoxification, we see significant increases throughout the whole posterior parietal cortex, including the precuneus, and the hyperactivity in the precuneus remains, even after protracted detoxification. This poses a challenge—it's much easier to interpret decreases in activity than increases. The precuneus is an area that basically has been found to regulate the levels of arousal.

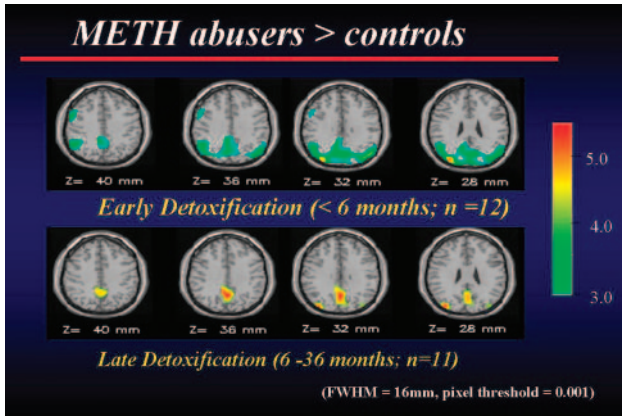

FIGURE 13. Comparison of metabolic activity in brain images from methamphetamine abusers during early and protracted detoxification with brain images of control subjects.

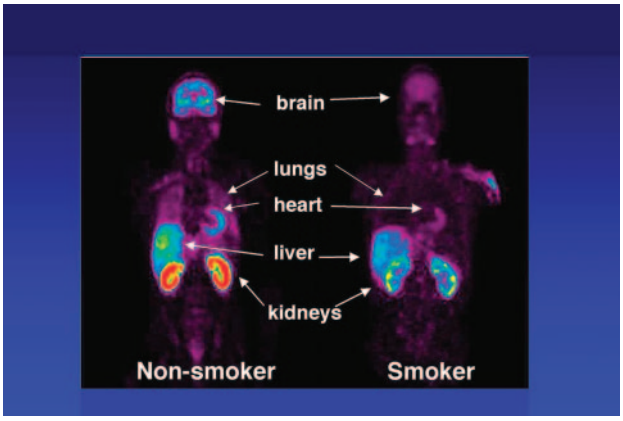

FIGURE 14. Cigarette smokers have a dramatic reduction in the concentration of monoamine oxidase not only in their brains but throughout their bodies.

When an individual is in a coma, for example, this area becomes extremely hypoactive. The greater the alertness, the greater the activity in this brain region. Indeed, anesthesiology studies have shown that the depth of anesthesia varies inversely with the activity in the precuneus. The greater the depth of anesthesia, the lower the activity in precuneus; the shallower the anesthesia, the greater the activity in this brain region. Looking at the seemingly paradoxical images of increased activity in the precuneus led me to speculate that if this area is important for arousal, then these individuals should have serious difficulty falling asleep and significant sleep disturbances. Do they? I don't know. No one has looked at this question. Clinicians have made anecdotal comments about methamphetamine abusers reporting sleep disturbances, but no one has systematically looked at this issue. I'm presenting this possibility, not because I know the answer to the question, but because it is an example of one of the many ways in which imaging can alert us to the consequences of drugs of abuse and point toward consequences that may have not been recognized.

Drugs target not only the human brain but are distributed throughout the entire body. As a result, they contribute to morbidity and mortality in a wide variety of diseases. Of utmost concern has been nicotine, because it's a major contributor to lung cancer. But it's also recognized that smokers have a much higher probability of developing cancers in many other areas of the body. This study by Joanna Fowler and colleagues at BNL illustrates the power of imaging technology, in this case PET technology, to provide us with mechanisms that can help us understand the adverse consequences of drugs. These studies assessed the effects of cigarette smoke on the concentration of monoamine oxidase in the human body. Monoamine oxidases are important in the brain to metabolize to catecholamines and regulate their concentrations. In the body, monoamine oxidases are important in helping to detoxify substances. In Fig. 14, you see the concentration of monoamine oxidase B in a normal person: high levels in the brain, kidney, heart, and lower levels in the lung. On the right is the concentration of monoamine oxidase B in a cigarette smoker—the image speaks for itself. Cigarette smokers have a dramatic reduction in the concentration of this enzyme not only in their brains but throughout their bodies. Nicotine is not the cause of this effect; instead, it is brought about by one of the chemicals in cigarette smoke. It is widely believed that the reason that cigarette smokers are at high risk for cancer of the lung is because carcinogenic compounds in smoke accumulate in the lung. These data indicate that the chemicals in smoke end up not only in the lungs but throughout the entire body, providing an explanation as to why a wide variety of cancers (bladder, pancreas, kidney) are much more frequently present in cigarette smokers than in nonsmokers.

Conclusion

In the field of drugs of abuse, multiple studies have shown that drugs of abuse affect genes, protein expression, neuronal circuits, and behavior, and, of course, have social consequences. However, these studies by themselves cannot explain the process of addiction. Part of the challenge is to integrate all that we know and have learned across the different levels of analysis. I have provided you with some examples that indicate that nuclear medicine imaging technologies are tools that allow us to do just that. We can now use imaging technologies to investigate how genes affect protein expression, how protein expression affects neurobiology, how neurobiology affects behavior, and how that, in turn, affects social interactions. But we can also begin to use imaging technologies as I illustrated in the study by Morgan to reverse the investigation and study how the environment, such as social factors, can modify elements of neurobiology, such as protein expression. This knowledge is extremely important. As we gain more information about how genes make individuals more vulnerable or more protected, this knowledge will allow us to perform interventions to protect those most at risk. Ultimately, predetermination does not mean predestination. And, it is in our capacity now to develop the knowledge that will allow us to identify and protect those who are most vulnerable.

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